

B. The Claims Are Definite

The Action rejects all pending claims as being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. In particular, the Action asserts that the recitations "aberrant alternate splice form of human glucocorticoid receptor (GR β)", "genetic changes", "altered GR β expression" and "changes outside" are unclear. The Action further asserts that claim 2 is indefinite for containing an improper Markush grouping and that claims 1-5 are indefinite for omitting essential elements. Applicants respectfully traverse.

1. The Claim Terms Are Definite

The Action appears to take the position that at least the indefiniteness of the phrases "aberrant alternative splice form" and "altered GR β expression" stems from the lack of a sequence listing providing the normal sequences of the gene and protein. Applicants note that nucleotide and amino acid sequences for GR β (SEQ ID NO:1 and SEQ ID NO:2, respectively) and for GR α (SEQ ID NO:3 and SEQ ID NO:4, respectively) have been provided in a sequence listing submitted herewith. Furthermore, references to SEQ ID NOs have been inserted in the specification and claims. It is believed that these amendments fully address the Action's concerns with respect to the indefiniteness at least of the phrases "aberrant alternative splice form" and "altered GR β expression". Furthermore, it is submitted that the insertion of SEQ ID NOs, as suggested by the Examiner, does not change the scope of the claims whatsoever. Thus, it is believed that according to the Federal Circuit's recent opinion in *Bose v. JBL*, 61 U.S.P.Q.2d 1216 (Fed. Cir. 2001), Applicants have not surrendered any rights to equivalents of the claimed subject matter.

With respect to the phrases "genetic changes" and "changes outside", Applicants maintain that the meaning of these phrases is well known to the skilled artisan. Nevertheless, simply to progress the case to allowance, claims 3 and 4 have been cancelled herein. Thus, the rejection based on the indefiniteness of the phrases "genetic changes" and "changes outside" is moot.

2. *Claim 2 Contains a Proper Markush Group*

The Action asserts that claim 2 is indefinite for containing an improper Markush grouping. According to the Action, the Markush group recited in claim 2 includes both methods and non-methods. Without further explanation or reasoning, the Action states that "denaturing gradient gel and single-stranded conformation polymorphism (SSCP) are not methods." Applicants respectfully disagree.

There are a number of techniques commonly used to detect variations in DNA sequences, and these are often used to screen for possible gene mutations. These techniques are well known by those skilled in the art (for example see Birren *et al.*, 1998; pp287-384 and Strachan & Read, 1996; pp. 367-399). Among the electrophoretic mobility alteration methods described in Birren (*see* Table 1, p. 289; attached hereto as Exhibit A) are: single-strand confirmation polymorphism (SSCP), denaturing gradient gel electrophoresis (DGGE), restriction enzyme fingerprinting, chemical cleavage of mismatches (CCM), constant denaturant gel electrophoresis (CDGE), and nondenaturing gel mismatch detection.

In SSCP, specific regions of normal and disease genes are amplified by PCR and loaded onto nondenaturing polyacrylamide gels. Single stranded DNA folds upon itself, and its electrophoretic migration is based on its sequence and length. Changes in DNA sequence

are often identified by alterations in the DNA fragment mobility. DNA sequencing of fragments with altered mobilities identifies specific nucleotide changes.

In DGGE, DNA duplexes migrate through an electrophoretic gel with a gradient of denaturant (chemical or temperature). Migration of the DNA duplex the gel continues until the two strands dissociate, and further migration of this denatured DNA is inhibited. Thus, clearly both SSCP and DGGE are methods, known by those skilled in the art, that can detect a single nucleotide change through altered gel electrophoretic mobility.

3. *The Claims Are Complete*

The Action further asserts that all pending claims are incomplete for omitting essential elements. The Action suggests that an acceptable method claim contains three sections: 1) a preamble, 2) method steps that clearly define what is to be done in each step, and 3) a conclusion that what was stated in the preamble was achieved. The Action seems to imply that Applicants are required to explain how to accomplish the detecting and how to measure the defect.

In light of the Examiner's suggestion to format the claims into three sections, Applicants have amended the claims to put them into a more readable format. Thus, claims 1 and 5 now include the following three sections suggested by the Examiner: 1) a preamble, 2) method steps that clearly define what is to be done in each step, and 3) a conclusion that what was stated in the preamble was achieved. It is believed that all sections were inherently present in the claims as filed so that the amendments do not narrow the intended scope of the claims under *Bose*. Applicants have not included a detailed explanation as to how the detecting is done or how the defect is to be measured because it is believed to be unnecessary.

It is not the role of the claims to provide a self-contained explanation of every step. *S3 Inc. v. nVIDIA Corp.*, 59 U.S.P.Q.2d 1745 (Fed. Cir. 2001). The Federal Circuit recently explained that the purpose of the claims is simply to state the legal boundaries of the patented invention. The fact that some terms in the claim are hard to understand when viewed without benefit of the specification does not necessarily render the claim indefinite. *S3 Inc.*, 59 U.S.P.Q.2d at 1748. If the claims contain a term or terms that would be readily recognized and understood by persons skilled in the art, they satisfy the requirements for definiteness.

In *S3*, nVIDIA argued that the term "selector" as used in the application was indefinite because the electronic structure of the selector and the details of its electronic operation were not described in the specification. *S3* provided evidence that a selector is a standard electronic component whose structure is well known in the relevant art. *Id.* at 1749. The Federal Circuit stated that "patent documents need not include subject matter that is known in the field of the invention and is in the prior art, for patents are written for persons experienced in the field of the invention." *Id.* (citing *Vivid Technologies, Inc. v. American Science and Engineering, Inc.*, 200 F.3d 795, 804, 53 U.S.P.Q.2d 1289, 1295 (Fed. Cir. 1999)). Likewise, in the present invention, it is submitted that the term "detecting" as used in the claims and specification would be readily understood by the skilled artisan and that techniques for accomplishing the detecting step are well known to the skilled artisan so that he would immediately understand the metes and bounds of the claim. Thus, it is believed that steps "disclosing how the 'detecting' is done" or "how the defect is measured" are unnecessary in light of well settled patent law.

In light of the foregoing arguments, Applicants respectfully request that the indefiniteness rejections be withdrawn.

C. The Claims Are Enabled

The Action next rejects claims 1-5 under 35 U.S.C. § 112, first paragraph as containing subject matter which was not described in the specification in such a way as to enable the skilled artisan to make and/or use the invention. Much of the Action's reasoning appears to be very similar to the indefiniteness rejection addressed in Section B.3. above. That is, the Action takes the position that the specification lacks written description for how to use the assays listed to diagnose glaucoma, how to detect genetic changes in the GR gene leading to altered GR gene GR β expression, how to determine if an agent that interacts with GR β is useful for treating glaucoma, what defects in the GR gene are indicative of the presence of glaucoma, what genetic changes in or outside the GR gene lead to altered GR β expression and how these changes are indicative of the presence of glaucoma, and how an agent that interacts with GR β or alters its expression is indicative of the presence of glaucoma. The Action further states that the specification and prior art lack experimental detail or data to support the statement in the specification that elevated intraocular pressure associated with POAG may be due to the aberrant expression of GR β in the trabecular meshwork. The specification is also said to lack an explanation of the mechanism of GR β interaction with GR α , how this relates to their interaction with glucocorticoids and their involvement with the onset of glaucoma. For these reasons, the claims are said to lack enablement within the meaning of the statute. Applicants respectfully traverse.

Applicants reiterate that a patent need not disclose what is well known in the art. *In re Wands*, 858 F.2d 731, 735, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988). In fact, it is preferable that what is well known in the art be omitted from the disclosure. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 U.S.P.Q. 81 (Fed. Cir. 1986) (citing *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 U.S.P.Q. 481, 489 (Fed. Cir. 1984)). In this case, the artisan skilled in the field of diagnosis of diseases using genetic information would be well aware of the techniques for detection of genetic changes and defects and would understand the phrases "genetic changes in the GR gene", "genetic changes outside the GR gene" and "altered GR β expression." Moreover, the skilled artisan would be able to make the connection between such altered expression in the trabecular meshwork and a diagnosis of glaucoma.

The specification explains that it was the present inventors who discovered that the trabecular meshwork (TM) of glaucoma patients expresses both GR β and GR α whereas the TM of non-glaucomatous patients expresses only GR α . Spec. page 2, lines 9-12. Thus, the skilled artisan would reasonably conclude that detection of GR β in the TM of a patient reveals the presence of glaucoma. The Action seems to imply that since the prior art doesn't provide any corroboration for the inventors' discovery that glaucomatous TM cells express GR β while non-glaucomatous TM cells do not, then the invention is not enabled. This reasoning fails to establish a *prima facie* case of non-enablement.

It is well settled patent law that the first paragraph of § 112 requires nothing more than objective enablement. *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971). This objective enablement may be provided through broad terminology or illustrative

examples. *Id.* The PTO bears the initial burden, in rejecting a claim under the enablement requirement of § 112, to set forth "a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application." *Wright*, 999 F.2d at 1561-62 (citing *Marzocchi*, 439 F.2d at 223-24, 169 USPQ at 369-70). The Action essentially attempts to punish Applicants for being the first to discover the differential expression of GR β in glaucomatous TM cells and for filing a patent application directed to their discovery before anyone else reported the finding in the literature.

The inventors include herewith as Exhibit B copies of pages from a laboratory notebook belonging to inventor Robert J. Wordinger, documenting the discovery of the differential expression of GR β in glaucomatous TM cells. The dates on the laboratory notebook pages are redacted, but the inventors state herein that the experiments were performed prior to the earliest priority date of the application, December 5, 1996. Page one of Exhibit B illustrates that glucocorticoid receptor primers recognize GR α and GR β . Page two of Exhibit B illustrates that GR β is only expressed in glaucomatous trabecular meshwork (GTM) samples (lanes 5, 6, 7) and that it is not induced by dexamethasone (DEX) (lanes 9 and 11). Page three of Exhibit B illustrates that GR β is expressed in two GTM cell lines and in one non-glaucomatous trabecular meshwork (NTM) sample. However, the occurrence of GR β in the one NTM sample was only observed in one NTM cell line on one gel and the results were not repeatable. Page four of Exhibit B illustrates that GR β was expressed in two GTM cell lines. No bands were observed in normal cell lines or in one GTM cell line.

The Action further asserts that a lack of description of the mechanism of GR β interaction with GR α , how it relates to their interaction with glucocorticoids and their involvement with the onset of glaucoma must lead to a conclusion of non-enablement. The Action seems to take the position that the specification does not describe how to use the invention within the meaning of § 112, first paragraph because it does not describe how it works. Applicants submit that this is an improper basis for a rejection based on a failure to satisfy the how to use requirement of § 112, first paragraph. Generally, evidence of a biological or pharmacological activity of a compound, such as a gene sequence or protein, will be relevant to an asserted use, such as diagnosis of a disease, if there is a reasonable correlation between the activity in question and the asserted utility. See MPEP § 2107.03(I), p. 2100-43 (August 2001) (citing *Cross v. Iizuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985); *In re Jolles*, 628 F.2d 1322, 206 U.S.P.Q. 885 (CCPA 1980); *Nelson v. Bowler*, 626 F.2d 853, 206 U.S.P.Q. 881 (CCPA 1980)). This reasonable correlation may be presented as statistically relevant data establishing the activity of the compound, arguments or reasoning, publications, or any combination of these. The MPEP explains that "the applicant does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty, nor does he or she have to provide actual evidence of success in treating humans where such a utility is asserted. Instead, as the courts have repeatedly held, all that is required is a reasonable correlation between the activity and the asserted use." MPEP at 2100-43 (citing *Nelson*, 626 F.2d at 857, 206 U.S.P.Q. at 884).

Applicants have shown that GR β is expressed in glaucomatous TM cells and that it is not expressed in non-glaucomatous TM cells. One of skill in the art would reasonably conclude that the presence (activity) of GR β in a sample containing TM cells from a patient indicates a glaucomatous condition. The Action provides no evidence that this conclusion is unreasonable. Therefore, it is believed that the claims are adequately enabled.

In light of the foregoing arguments, Applicants respectfully request that the rejection based on lack of enablement be withdrawn.

D. Conclusion

This is submitted to be a complete response to the outstanding Action. Based on the foregoing arguments, the claims are believed to be in condition for allowance. A notice of allowability is therefore respectfully requested.

The Examiner is invited to contact the undersigned attorney at (817) 551-4321 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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APPENDIX A – Marked-up Version of Claims and Specification

Surprisingly, it has been found that cultured human trabecular meshwork cell lines derived from glaucomatous donors express mRNA for both an alternate splice form of the human glucocorticoid receptor (GR β) (SEQ ID NO:1), as well as the normal glucocorticoid receptor (GR α) (SEQ ID NO:3), whereas normal TM cell lines only express mRNA for GR α . It is believed that the elevated intraocular pressure associated with primary open-angle glaucoma may be due to the aberrant expression of GR β (SEQ ID NO:2) in the trabecular meshwork. Therefore, determining that an individual abnormally expresses GR β in their trabecular meshwork or other tissues can lead to a diagnosis of glaucoma. Also, this discovery can be used to determine whether agents have therapeutic value in treating glaucoma by determining whether they interact with GR β (SEQ ID NO:1) or alter the expression of GR β (SEQ ID NO:2). This can be done using ligand binding assays or GR β functional assays.

1. (twice amended) A method for diagnosing glaucoma in a person, [which comprises detecting aberrant alternate splice form of the human glucocorticoid receptor (GR β) expression or defects] said method comprising the steps:

(c) obtaining a biological sample from said person; and

(d) analyzing said sample for expression of SEQ ID NO:2;

wherein aberrant expression of SEQ ID NO:2 or a defect in a GR gene [which encodes GR β] encoding SEQ ID NO:2 as compared to SEQ ID NO:1 indicates a diagnosis of glaucoma.

3. CANCELLED

4. CANCELLED

5. (amended) A method for determining whether an agent is useful for treating glaucoma, said method comprising the steps:

(d) obtaining a composition comprising SEQ ID NO:1 or SEQ ID NO:2;

(e) admixing said composition with an agent; and

[by] determining whether [it] the agent interacts with [GR β] SEQ ID NO:2 or alters the expression of [GR β] SEQ ID NO:2.

APPENDIX B – Currently Pending Claims

1. (twice amended) A method for diagnosing glaucoma in a person, said method comprising the steps:

- (e) obtaining a biological sample from said person; and
- (f) analyzing said sample for expression of SEQ ID NO:2;

wherein aberrant expression of SEQ ID NO:2 or a defect in a GR gene encoding SEQ ID NO:2 as compared to SEQ ID NO:1 indicates a diagnosis of glaucoma.

2. The method of claim 1 wherein GR gene defects are detected by a method selected from the group of assays consisting of: restriction fragment length polymorphism (RFLP), single-stranded conformation polymorphism (SSCP), polymerase chain reaction (PCR), denaturing gradient gel, allele specific oligonucleotide ligation, and allele specific hybridization.

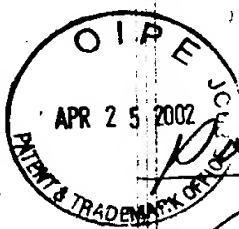
5. (amended) A method for determining whether an agent is useful for treating glaucoma, said method comprising the steps:

- (f) obtaining a composition comprising SEQ ID NO:1 or SEQ ID NO:2;
- (g) admixing said composition with an agent; and

determining whether the agent interacts with SEQ ID NO:1 or alters the expression of SEQ ID NO:2.

Abe:

Hope these Copies are OK!



Page 1 (#256) - Glucocorticoid
receptor - primers recognize
GR α and GR β .

Page 2 (#254) GR- β - only expressed
in GTM samples (e.g. lanes 5, 6 & 7)
Not induced by DEX (lanes 9 & 11).

Page 3 (#258) GR- β - Expressed in
2 GTM cell lines; 1 NTH cell
line

Page 4 (?) GR- β - Expressed in
2 GTM cell lines. No bands
in normal cell lines or 1 GTM
cell line

Conclusions - GR- β was expressed
in 4 GTM cell lines (e.g. GTM-23;
GTM-48; GTM-75; GTM-85). Only saw
it in 1 NTH cell line on 1 gel
not repeatable.

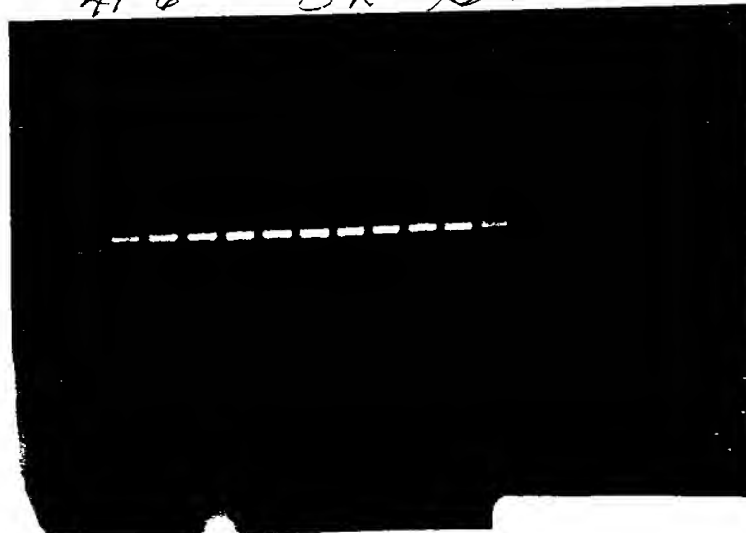
EXHIBIT A

Glucocorticoid receptor PCR 41-6
Master Mix - Previously made
on 9-16, 9-18, & 9-20

Lanes	1	2	3	4	5	6	7	8	9	10	11	12	13
	HTM-60												
	HTM-24p.					GTM-48-77p.							
	HTM-184p.					GTM-75 854p.							
	HTM-544p.					HTM-24p. Control							
	HTM-804p.					HTM-24p. DEX-14 days							
	GTM-23D-67p.					HTM-544p. Control							
						HTM-544p. DEX-14 days							
						Control							

Result: These primers recognize both α & β isoforms

41-6- GR- General



bp = 626

EXHIBIT B

Robert J. Winkler

PCR - # 43.6
Glucocorticoid Receptor - 13

Subunit

Crystallizing Temp. 55°C

- | | | |
|------------|------------------------------|--|
| lane 1. 6M | 6. 6TM-23 | |
| 2. 2yr | 7. 6TM-48 | |
| 3. 18yr | 8. 6TM 85 | |
| 4. 54yr | 9. 4TM-2 yr - 14 day cont'd | |
| 5. 80yr | 10. 14TM-2 yr - 14 day - DEX | |
| | 11. 4TM-54 - 14 day cont'd | |
| | 12. 14TM-54 - 14 day DEX | |
| | 13. Control | |

Robert M. Kerkling

GR-B

10-4-96

43-6

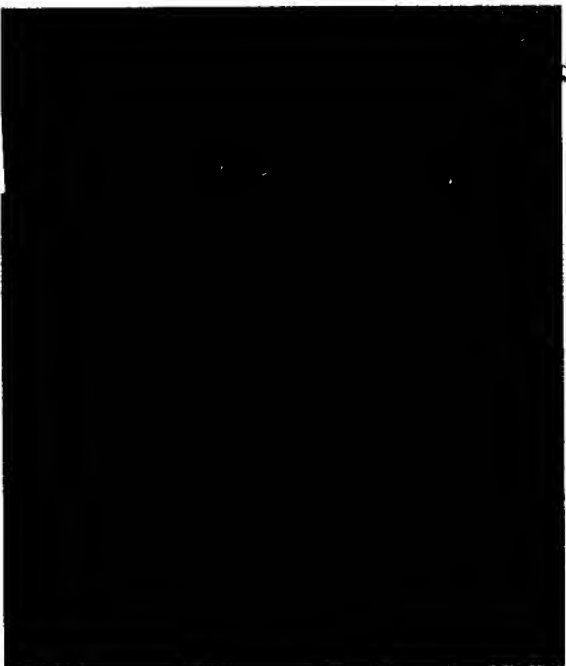
scale down!

8R-B1 - Yellow River, Nevada
Overnight's Junior Primaries

lane	1 - 6 yrs	5	STM 48
	2 - 54 yrs	6	STM - 85 yrs
	3 - 80 yrs	7	Con. Tr. 1
	4 - STM 230		

* PER Program were added
 after all key mistake - results
 Run - 46-6
 RUN # 46-6

Robert M. Madsen



6P-321

- PER Band was removed in
 lane 5 (STM 48) and front band
 in lane 6 (STM 85 yrs). No band
 in normal lane lanes 8 & lane 11
 (STM-230)

Note-Saved only Product # 5 (2022) 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100

RECEIVED

APR 11 2000

TECH CENTER 1600, 2900

254

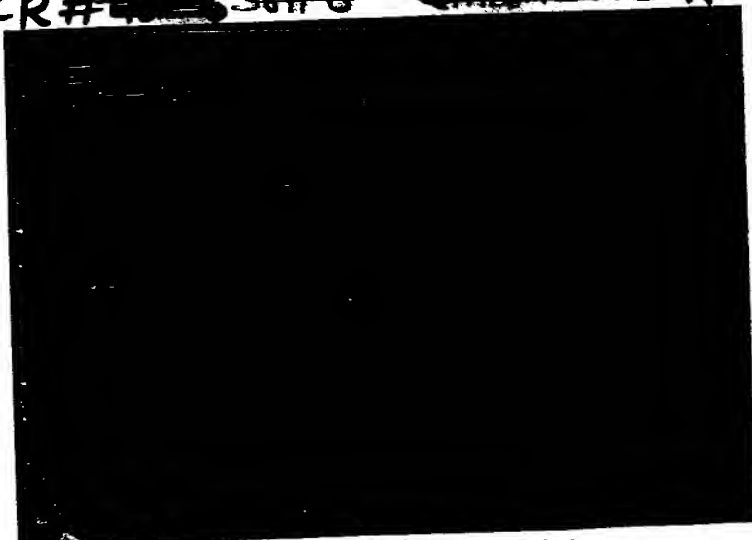
PCR # 39-6
Lone # 321

PCR Run 39-6 Glucocorticoid
Receptor - 3. GR-32

Lone # - Ladder	Lone #6 GTM-48
1 - 6M	57 GTM-75
2 - 2yr	58 2yr
3 - 54yr	59 2yr-DEX
4 - 80yr	60 54yr
5 - GTM-23	61 54yr-DEX

Annealing temp = 55°C
Run Agarose Gel 9/23/96

39-6
PCR # ~~4~~ 3616 ~~GR-13~~



Robert J. Heringer

9/23/96

LP = 321